physicians and patients. One of the challenges for informatics will be to provide patients with information of sufficient quality and the knowledge of how to integrate it with the skills of their physicians. Analogously, the information base and skill set provided to clinicians must recognize and complement the new role of patients.

Evaluating Outcomes

Medical informatics develops products that affect clinical practice and will potentially affect the outcomes of clinical care. The evaluation of these new technologies must go beyond examining their premises or exploring the various nooks and crannies of their logic, notwithstanding the complexities of even those limited goals. Clinicians and informaticians (two broadly overlapping sets of professionals) must examine how these programs, systems, and theories change the results of health care. If health outcomes are improved and costs are lowered—not an unreasonable expectation for these new technologies—then arguments about cost-effectiveness become moot. We need be concerned about cost-effectiveness only if costs increase and health outcomes improve. In that case, we might estimate how much we must spend for each unit increase in health and compare that marginal ratio with our willingness to pay for health.

Because medical informatics concerns understanding information and how we interact with it, clinicians and informaticians must communicate if the field is to progress. This series in the *Journal* is an important step. The real challenge facing medical informatics is not in developing new applications, building newer and faster computers, delivering more bits per second to the desktop, or even collecting, organizing, and validating information. Rather, our challenge is to maintain an open dialogue among informaticians, clinicians, and patients. To succeed will require constant effort; to fail will doom us to losing control of our destiny.

STEPHEN G. PAUKER, MD
JAMES E. STAHL, MD
New England Medical Center
Boston, Massachusetts

REFERENCE

1. Altman RB. Informatics in the care of patients: ten notable challenges. West J Med 1997 Feb; 166:118–122

A Fragile Enterprise

The opposite of a correct statement is a false statement. But the opposite of a profound truth may well be another profound truth.

NIELS BOHR

THE BASIC TENETS of heredity have seemed clear for more than 100 years, and until recently, it was thought that the inheritance of most familial disorders could be understood in terms of the principles articulated by Mendel and subsequently refined by others. Genetic diseases should be transmitted in families in patterns consistent with autosomal dominant, autosomal recessive, or X-linked modes of inheritance. In the past few years, however, there has been an explosion of knowledge relating to human conditions that are inherited in nonmendelian ways. These newly described genetic mechanisms include mitochondrial inheritance in which traits may be exclusively matrilineally inherited, genomic imprinting in which genes contributed by a father and mother are not equally expressed in the offspring, and genomic instability in which the immutable transmission of DNA sequence from parent to child turns out to lack the fidelity we had expected. The so-called fragile X syndrome, which is reviewed by Hagerman elsewhere in this issue of the *Journal*,[1] is in the last category.

The fragile X syndrome is the most common inherited cause of mental retardation. The first clear pedigree of a family with this disorder was reported in 1943. The characteristic cytogenetic finding was described in 1969, but it was not until 1991 that the responsible gene *FMR1* (for fragile X mental retardation) was identified and characterized.[2] It should be pointed out that although most cases of X-linked mental retardation with a fragile site visible on karyotype are due to abnormalities of the *FMR1* gene, some families have defects in other genes nearby. The normal protein product of the *FMR1* gene binds to certain RNA molecules, but its function has not been fully defined. It does seem, however, that the loss of function of the *FMR1* protein is responsible for most of the phenotypic features of the fragile X syndrome. For example, when a small mutation destroys the ability of the *FMR1* protein to bind to RNA, or when *FMR1* gene function is disrupted in mice, most of the features of the disorder are present. In the vast majority of human patients with the fragile X syndrome, however, the mechanism that leads to the loss of function of *FMR1* is different. The *FMR1* gene is one of a growing family of genes found to contain within its structure a repeating series of nucleotides. In this case, the sequence is $(CGG)_n$. The repeat is located within the so-called 5′ untranslated portion of the gene, which is transcribed from DNA into messenger RNA, but does not actually encode any amino acids in the final protein product. In normal persons, the number of CGG repeats in the *FMR1* gene ranges between 6 and 52. In patients with the full-blown fragile X syndrome, the number of repeats is greater than 230 and may be more than 1,000. In ways that are not yet fully understood, the expanded repeats shut off expression of the gene (associated with the methylation of nearby controlling DNA sequences) and lead to an altered chromatin structure of that region of the X chromosome. This results in the cytogenetic appearance of a fragile site.

Recognition of the expansion of a trinucleotide repeat in this gene in patients with the fragile X syndrome not only opens the door to understanding the mechanism of control of *FMR1* expression, but also provides insight into the processes by which alterations in the number of repeats may arise from one generation to the next. For some time, we have known of clinically normal men who have

had grandsons with the fragile X syndrome. As might be expected for an X-linked trait, these "transmitting males" pass the abnormality through their daughters and not their sons. Transmitting males have been said to have a "premutation" that is activated to a full mutation after passing through a female intermediate. Molecular studies now show that these transmitting males have a partial expansion of the CGG copy number in *FMR1* to the range of 60 to 200. They will donate this partially expanded CGG region as part of the X chromosome that they contribute to all of their daughters, but typically, the copy number remains unchanged. These partial expansions are, however, further amplified in a high percentage of these women during oogenesis, giving rise to the full mutation number of CGG repeats in the grandsons who then have the complete syndrome. Thus, the results of molecular analyses in families with the fragile X syndrome have explained aspects of the inheritance of the syndrome that were not previously understood.

In addition to clarifying the basis of transmitting males, molecular studies of the *FMR1* gene are elucidating the basis for the phenotypic variation in the fragile X syndrome. As many as a third of female carriers of the full-blown fragile X-CGG expansion will have some clinical symptoms, including mild mental retardation and premature ovarian failure. The reasons for this appear to be related to the phenomenon of X chromosome inactivation. True carrier females will have a copy of FMR1 that contains the expansion, is overmethylated, and cannot be expressed. The copy of *FMR1* on their other X chromosome will be structurally normal, but about half of their cells will be rendered quiescent through the process of X chromosome inactivation. Thus, such females have two populations of cells, one with normal amounts of *FMR1* and the other in which *FMR1* protein will be absent. Depending on whether the fraction of deficient cells is exactly half or not, and depending on the ratios of deficient and sufficient cells in various tissues (for example, the central nervous system), the carrier female may or may not have clinical symptoms. In males who are the offspring of women with premutation lengths of CGG repeats, mosaicism may occur so that some of their cells have undergone further expansion of the CGGs in *FMR1*. In other cells, the CGG copy number remains at the premutation level. The premutation *FMR1* genes are not methylated and presumably are expressed, but the full mutation-length CGG expansion genes are methylated and shut off. Thus, these males also have cellular mosaicism, which can have variable clinical consequences.

In addition to providing a much better understanding of the pathogenesis of the fragile X syndrome, the recent molecular advances have enhanced the study of the epidemiology of this disorder and its clinical diagnosis. The older cytogenetic tests, although still useful, are subject to several vagaries. The visualization of fragile sites is highly dependent on tissue culture and laboratory conditions as well as the skill and experience of the technician. The molecular tests are less ambiguous, so it has been possible to understand better the actual incidence of the fragile X syndrome and its full phenotypic spectrum. The availability of good diagnostic tests has already helped in the diagnosis of new patients and in giving genetic counseling to family members at risk for transmitting the disease. Prenatal diagnosis using fetal DNA derived from amniocytes, chorionic villous biopsy, or embryo biopsy is feasible and offers options for families in which this syndrome occurs. In the future, large-scale screening of newborns can be considered, but only after it is clear that early recognition of the disease would lead to some beneficial intervention to the child or the family. Ultimately, a more thorough understanding of the role of *FMR1* protein may lead to strategies for therapeutic intervention, although this may need to occur early in development. In the meantime, the summary of clinical findings and management strategies provided in the article by Hagerman should be read by all pediatricians and other clinicians who are likely to encounter patients with this common clinical problem because it provides much useful information.

LARRY J. SHAPIRO, MD
W.H. and Marie Wattis Distinguished Professor
Chair, Department of Pediatrics
University of California, San Francisco,
School of Medicine
San Francisco, CA 94143

REFERENCES

1. Hagerman RJ. Fragile X syndrome—Molecular and clinical insights and treatment issues. West J Med 1997; 166:129–137

2. Verkerk AJ, Pieretti M, Sutcliffe JS, et al. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell 1991; 65:905–914

Improving Quality Improvement: A Data-Driven Assessment

THE INEXORABLE search for quality in health care is embedded in the Hippocratic oath. Modern approaches to quality analysis in health care, however, owe as much to business reengineering strategies as they do to the scientific method. Although the literature contains many examples of successful quality interventions, it is also littered with failures. The promise of substantial improvements in quality through integrated systems and national practice guidelines has yet to be fully realized. Despite these limitations, many organizations have realized important improvements in care resulting from quality improvement activities, and a wide array of external organizations, from health care purchasers to accrediting agencies, are asking for quality information. Given this national backdrop, what are the implications of the research by Goldman and colleagues, reported elsewhere in this issue,[1] for evaluating previous quality initiatives and for identifying possibly successful strategies for future quality-related activities?

The history of modern quality improvement begins with physicians.[2] At the turn of the century, Ernest Codman, MD, evaluated the care of patients at Massachusetts